To: dkrewski@uottawa.ca[dkrewski@uottawa.ca]; Rusyn, Ivan[IRusyn@cvm.tamu.edu]; Robert Baan[BaanR@visitors.iarc.fr]; Cogliano, Vincent[cogliano.vincent@epa.gov]; Kavlock, Robert[Kavlock.Robert@epa.gov]
Cc: straif@iarc.fr[straif@iarc.fr]; cportier@mac.com[cportier@mac.com]
From: Bucher, John (NIH/NIEHS) [E]
Sent: Sun 7/17/2016 4:27:54 PM
Subject: Re: Tumour-site Concordance and Mechanisms of Carcinogenesis

Robert and all involved,
Thanks for all the efforts at pulling this together. I had a few additional comments to those of Ivan on the consensus statements for your consideration.
Best, John

Comments on concordance statement

1. There's an appearance of discordance between statement two concerning the lack of melanoma response in rats and mice, following statement one that all adequately studied human carcinogens are carcinogens in animals. This may be resolved in a footnote.

2. Statements 3 and 4 don't seem to rise to the level of one and two. Perhaps recommendations could follow concordance statements, separated by a header.

3. Statement seven seems to be a simple statement of fact that might be better placed as paragraph 2 in the introduction. Also the last sentence in 7 could use some work.

4. Statement 8 contains the first mention of key characteristics. This could benefit by a mention in the introduction as an outcome of the meetings, and then statement 8 could stand as an endorsement of their usefulness.

5. Statement 9 could be stronger if it indicated whether there was general concordance of mechanism between animals and humans, in addition to the existence of human data. Genotoxicity alone should support this.

6. It's not made clear in statement 11 whether human carcinogens individually or collectively act through multiple mechanisms. Also, this statement seems to include several distinct topics that may deserve individual treatment. Statement 13 covers some of the same ground, and might be combined with a disentangled 11 where appropriate.

From: Daniel Krewski <dkrewski@uottawa.ca>
Date: Saturday, July 16, 2016 at 5:37 PM
To: "Rusyn, Ivan" <IRusyn@cvm.tamu.edu>, Robert Baan <BaanR@visitors.iarc.fr>, "Cogliano.Vincent@epamail.epa.gov" <Cogliano.Vincent@epamail.epa.gov>, "kavlock.robert@epa.gov" <kavlock.robert@epa.gov>, "John R. Bucher" <bucher@niehs.nih.gov>
Cc: "straif@iarc.fr" <straif@iarc.fr>, Christopher Portier <cportier@mac.com>
Subject: RE: Tumour-site Concordance and Mechanisms of Carcinogenesis

Thanks for your positive comments, Ivan, and for your specific comments on the draft consensus statement.

Although Robert will be coordinating the response to all comments by the Workshop Participants, I've offered a few perspectives on some of your comments below (a pleasant way to pass the time sitting in Montreal airport on my way home from Lyon) . . .

Dan K.

From: Rusyn, Ivan [mailto:IRusyn@cvm.tamu.edu]
Sent: July-16-16 12:19 PM
To: Robert Baan <BaanR@visitors.iarc.fr>; Cogliano.Vincent@epamail.epa.gov; kavlock.robert@epa.gov; Daniel Krewski <dkrewski@uottawa.ca>; 'bucher@niehs.nih.gov' <bucher@niehs.nih.gov>
Cc: straif@iarc.fr; cportier@mac.com
Subject: RE: Tumour-site Concordance and Mechanisms of Carcinogenesis

Dear Robert,

Great job. Congratulations!

My comments on the consensus statement:

Item#5: I am concerned that replication of a tumor site is given so much weight. It is not required to reach "sufficient" evidence so we shall tone down this paragraph not to create an impression that IARC endorses a point of view that replication of the tumor site in animal studies is a requirement for the finding to be of concern.

Item #6: I suggest we add the following (or paraphrased) sentence at the end: "Thus, evidence streams other than human epidemiology will need to be relied upon to determine human cancer hazards."

Item #8: I am confused with "continue to develop" language about Key Characteristics. I believe we need not to have this part in the sentence and it should read: "The Workshop participants recommend that the IARC Monographs Programme use them in its evaluations of carcinogenicity." I believe what was intended here was for WGs to document the 10 KCs in future Monographs, rather than to modify the KCs per se – if the phrase "continue to develop" does not give this impression, some modification of the language along the lines you suggest would be appropriate.

Item #9: I am not sure what the message here is… It appears to be an odd trivia fact and should be either expanded to explain why this is important, or deleted. Robert and I had some discussion about this statement yesterday, based on the observation that Figure 4 in the mechanisms chapter suggests that similar KCs appear to be observed in humans and animals. However, as Figure 4 does not provide a direct comparison between humans and animals, I am preparing a modified version of this figure that will address this point directly. Depending on the outcome of this (easy to do) analysis, it may be possible to make a stronger statement about similar KCs being observed in humans and animals, which would further support the relevance of animal data in cancer risk assessment.

Item #10: I propose for consistency we amend the last sentence to read "…less-than-sufficient evidence in experimental animals."

Item #11: I am also not sure what the message is here. Invoking the wording of "adverse outcome networks" may not be without controversy as it may be interpreted as a not of endorsement to AOP concept by IARC. I suggest this paragraph is toned down to acknowledge that most, if not all, carcinogens act by multiple mechanisms and that greater understanding of molecular events leading to carcinogenesis will further enhance our ability to identify cancer hazards.

Item #13: Again, I would refrain from explicitly suggesting that the new "canon" of 10 Key Characteristics is a "living document". Of course it is, but we need not to state it so explicitly. I am concerned that providing such vagueness may open the door for the criticism of the current Key Characteristics as they have been used in several recent monographs… The less material we provide to our friends who publish newspaper articles about how IARC process is flawed, the better… In my humble opinion… Understanding your point being that we do not want to undermine the credibility of the 10 KCs by suggesting they should be revised in the future, I could suggest it may be 'bad luck' to have *thirteen* consensus statements!

Thank you!

Ivan

From: Robert Baan [mailto:BaanR@visitors.iarc.fr]
Sent: Friday, July 15, 2016 3:52 PM
To: banks@icgeb.org; frederick.beland@fda.hhs.gov; toxcon@earthlink.net; boslandm@uic.edu; bucher@niehs.nih.gov; caldwell.jane@epa.gov; Cogliano.Vincent@epamail.epa.gov; demarini.david@epa.gov; bice.fubini@unito.it; bdgold@pitt.edu; hecht002@umn.edu; k.hemminki@dkfz.de; mark.hill@rob.ox.ac.uk; drjameson@embarqmail.com; Agnes_Kane@Brown.edu; kavlock.robert@epa.gov;

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Cc: straif@iarc.fr; Jmricewas@aol.com; cphra@uottawa.ca; bullrich@utmb.edu; cportier@mac.com; workshops100+@iarc.fr
Subject: Tumour-site Concordance and Mechanisms of Carcinogenesis

Dear colleagues,

It has been a long time since we had contact; I hope you are doing fine.

I am pleased to announce the near completion of the project 'Tumour-site Concordance and Mechanisms of Carcinogenesis'. Some of you may remember the teleconference in December last year, during which it was decided to delete the numerical results (kappa-statistics) from the concordance analysis proposed by Dan Krewski and his team, leaving us the task of finding a different way to present the concordance data. During a second teleconference in February of this year, a small group of participants discussed a new proposal to present the data, based on the concept of 'overlap' of tumour sites between humans and experimental animals. This subgroup and the Ottawa team worked out a completely new version of the concordance analysis, with new Figures and Tables. We have greatly appreciated the input and efforts of all involved to arrive at this result.

Today we submit to you the corresponding documents for your approval. Also attached is the analysis of the mechanistic data, based on the 10 Key Characteristics.

Attached you will find the complete analyses on 'Concordance' and 'Mechanisms' in documents 1 and 7. The other documents contain late-incoming corrections, and show details on the data set on which the concordance analysis is based.

Finally, document 8 is a draft Consensus Statement that presents what we suggest to be the main conclusions and recommendations of the Workshop participants.

We hope you can endorse the Consensus Statement and the final results presented in the attached documents.

With your support, we will bring this project to a close.

I hope to hear from you, wishing you pleasant holidays.

With my best regards,

Robert